Access DB# 75009

CRFE

# SEARCH REQUEST FORM

**Scientific and Technical Information Center**

Requester's Full Name: Nirmal S. Bari Examiner # : _____ Date: 9/5/02
Art Unit: 1646 Phone Number 30 8 9435 Serial Number: 09/205 985
Mail Box and Bldg/Room Location: CM1 10E17 Results Format Preferred (circle): PAPER DISK E-MAIL
Mail room 10D17

**If more than one search is submitted, please prioritize searches in order of need.** mej

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Method of Inhibiting Osteoclast Activity

Inventors (please provide full names): Anderson & Galibert

Earliest Priority Filing Date: 12/23/96

***For Sequence Searches Only*** *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

1. Please search a polypeptide comprising:
a) SEQ ID NO: 2, 8, 1, 3
b) amino acids 1-213 of SEQ ID NO: 2
c) " 33-213 " " "
d) " 33-196 "

2. polypeptide comprising amino acids 30-213 of ~~SEQ ID NO~~ SEQ ID NO: 2 together with SEQ ID NO: 3 (Junction Protein)

Point of Contact:
Barb O'Bryen
Technical Information Specialist
STIC CM1 6A05 308-4291

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| STAFF USE ONLY | Type of Search | Vendors and cost where applicable |
|---|---|---|
| Searcher: BOB | NA Sequence (#) _____ | STN _____ |
| Searcher Phone #: _____ | AA Sequence (#) 9 | Dialog _____ |
| Searcher Location: _____ | Structure (#) _____ | Questel/Orbit _____ |
| Date Searcher Picked Up: _____ | Bibliographic _____ | Dr.Link _____ |
| Date Completed: 9-9-02 | Litigation _____ | Lexis/Nexis _____ |
| Searcher Prep & Review Time: 14 | Fulltext _____ | Sequence Systems Wisc. IG |
| Clerical Prep Time: _____ | Patent Family _____ | WWW/Internet _____ |
| Online Time: 03 | Other _____ | Other (specify) _____ |

PTO-1590 (8-01)

(
********** STN Columbus **********

FILE 'MEDLINE' ENTERED
FILE 'JAPIO' ENTERED
FILE 'BIOSIS'
FILE 'SCISEARCH'
FILE 'WPIDS'
FILE 'CAPLUS'
FILE 'EMBASE'
=> bio
L1 122149 BIO

=> s rank or rankl
L2 130256 RANK OR RANKL

=> l2 and bone
L3 4016 L2 AND BONE

=> l3 and bone loss
L4 309 L3 AND BONE LOSS

L5 309 L4 (10W) BONE LOSS

=> l4 and (cancer or myeloma or carcimoma)
L6 19 L4 AND (CANCER OR MYELOMA OR CARCIMOMA)

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 8 DUP REM L6 (11 DUPLICATES REMOVED)

=> d l7 ibib abs 1-8

L7 ANSWER 1 OF 8 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001396168 MEDLINE
DOCUMENT NUMBER: 21234913 PubMed ID: 11336917
TITLE: Osteoprotegerin inhibits osteoclast formation and ***bone*** resorbing activity in giant cell tumors of ***bone*** .
AUTHOR: Atkins G J; Bouralexis S; Haynes D R; Graves S E; Geary S M; Evdokiou A; Zannettino A C; Hay S; Findlay D M
CORPORATE SOURCE: Department of Orthopaedics,University of Adelaide, Adelaide, SA, Australia.
SOURCE: BONE, (2001 Apr) 28 (4) 370-7. Journal code: 8504048. ISSN: 8756-3282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712
AB Osteolysis is a common complication of tumors that arise in, or metastasize to, ***bone*** . The recent discovery of key regulators of osteoclast formation and activity, including receptor activator of nuclear factor of kappaB ligand ( ***RANKL*** ), ***RANK*** , and osteoprotegerin (OPG), may facilitate new treatment regimes for certain tumors associated with excessive ***bone*** ***loss*** . We recently showed that the stromal cells of osteolytic giant cell tumors (GCT) of ***bone*** express high levels of mRNA encoding ***RANKL*** , relative to mRNA for the ***RANKL*** antagonist, OPG, compared with the expression patterns of other lytic and nonlytic ***bone*** tumors. In this study, we found that expression of ***RANKL*** and OPG mRNA continued by the stromal element of these tumors in a constitutive manner for at least 9 days in the absence of giant cells. Immunostaining of unfractionated GCT cultured in vitro revealed punctate cytoplasmic/membranous staining for ***RANKL*** and both cytoplasmic and extracellular matrix staining for OPG in stromal cells. Giant cells (osteoclasts) were negative for ***RANKL*** staining, but stained brightly for cytoplasmic OPG protein. We also investigated the functional relevance of these molecules for GCT osteolysis by adding recombinant OPG and ***RANKL*** to cultured GCT cells. We found that OPG treatment potently and dose-dependently inhibited resorption of ***bone*** slices by GCT, and could also inhibit the formation of multinucleated osteoclasts from precursors within the GCT. These effects of OPG were reversed by stoichiometric concentrations of exogenous ***RANKL*** . These data indicate that both the processes of osteoclast formation and activation in GCT are promoted by ***RANKL*** . Therefore, GCT represent a paradigm for the direct stimulation of osteoclast formation and activity by tumor stromal cells, in contrast to the mechanisms described for osteolytic breast tumors and multiple ***myeloma*** . The demonstration of these relationships is important in developing approaches to limit tumor-induced osteolysis.

L7 ANSWER 2 OF 8 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001147960 MEDLINE
DOCUMENT NUMBER: 21063741 PubMed ID: 11121682
TITLE: Molecular control of ***bone*** remodeling and osteoporosis.
AUTHOR: Kong Y Y; Penninger J M
CORPORATE SOURCE: Division of Molecular and Life Science, Pohang University of Science and Technology, Pohang, Kyungbuk 790-784, South Korea.
SOURCE: EXPERIMENTAL GERONTOLOGY, (2000 Oct) 35 (8) 947-56. Ref: 36
Journal code: 0047061. ISSN: 0531-5565.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW) (REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315
AB Osteoprotegerin ligand (OPGL, TNFS11) and its receptor ***RANK*** (TNFRS11A) are essential for the development and activation of osteoclasts and critical regulators of physiological ***bone*** remodeling and osteoporosis. Production of OPGL by activated T cells can directly regulate osteoclastogenesis and ***bone*** remodeling. This may explain why autoimmune diseases, ***cancers*** , leukemias, asthma and chronic viral infections such as hepatitis and HIV result in systemic and local ***bone*** ***loss*** . OPGL is also the pathogenetic factor that causes ***bone*** and cartilage destruction and clinical crippling in arthritis. Inhibition of OPGL binding to ***RANK*** via the natural decoy receptor osteoprotegerin (OPG) prevents ***bone*** ***loss*** in postmenopausal osteoporosis and ***cancer*** metastases and completely blocks crippling in a rat model of arthritis. Moreover, OPG expression is induced by estrogen which provides a molecular explanation of postmenopausal osteoporosis in women.

L7 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:320185 BIOSIS
DOCUMENT NUMBER: PREV200100320185
TITLE: Osteoprotegerin (OPG) inhibits the development of osteolytic ***bone*** disease in the 5T2MM model of multiple ***myeloma*** .
AUTHOR(S): Croucher, Peter I. (1); Shipman, Claire M. (1); Perry, Mark J.; Lippitt, Jenny (1); Asosingh, Kewal; van Beek, Edwin J. R.; Van Camp, Ben; Russell, Graham G. (1); Dunstan, Colin; Vanderkerken, Karin
CORPORATE SOURCE: (1) Biochemical and Musculoskeletal Medicine, University of Sheffield, Sheffield UK
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 761a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Multiple ***myeloma*** (MM) is often associated with the development of osteolytic ***bone*** disease, the management of which is confined to the use of bisphosphonates. However, with improvements in our understanding of the mechanism of ***bone*** ***loss*** , novel therapeutic targets may be identified. Recent studies have shown that binding of the ligand for receptor activator of NF-kappaB ( ***RANKL*** ) to ***RANK*** , on osteoclast precursors, is essential for osteoclast formation. ***Myeloma*** cells also express ***RANKL*** suggesting that they may promote osteoclast formation directly. A soluble decoy receptor, OPG, has been identified that can bind to ***RANKL*** and prevent osteoclast formation. The aim of this study therefore was to determine whether an OPG fusion protein (Fc-OPG) could inhibit the development of lytic ***bone*** disease in a model of MM. 5T2MM murine ***myeloma*** cells were injected intravenously into C57BL/KaLwRij mice and the development of the disease monitored by measuring serum paraprotein. After 8 weeks all animals had a detectable paraprotein and were treated with Fc-OPG (25mg/kg, iv, 3 times/week) or vehicle for a further 4 weeks. All animals injected with 5T2MM cells developed ***bone*** disease characterised by radiological evidence of osteolytic lesions in the tibiae and lumbar vertebrae. Histomorphometric studies demonstrated that this was associated with a decrease in ***bone*** volume (BV/TV) in the proximal tibial metaphyses ($p<0.01$) and DXA analyses demonstrated a decrease in ***bone*** mineral density (BMD) in the tibiae and vertebrae. Treatment of 5T2MM-bearing mice with Fc-OPG prevented the development of lytic ***bone*** lesions in the tibiae and vertebrae ($p<0.01$, respectively). Treatment was also associated with a partial preservation of BV/TV in the tibial metaphyses ($p<0.05$) and an increase in both tibial and vertebral BMD ($p<0.001$, respectively). Fc-OPG had no effect on paraprotein levels or tumour volume. These data demonstrate that Fc-OPG inhibits the development of lytic ***bone*** disease in a model of established MM and may represent a new approach to the treatment of ***myeloma*** ***bone*** disease.

L7 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:25403 CAPLUS
DOCUMENT NUMBER: 132:235163
TITLE: Interactions between ***cancer*** and ***bone*** marrow cells induce osteoclast differentiation factor expression and osteoclast-like cell formation in vitro
AUTHOR(S): Chikatsu, Noriko; Takeuchi, Yasuhiro; Tamura, Yasuhiro; Fukumoto, Seiji; Yano, Kazuki; Tsuda, Eisuke; Ogata, Etsuro; Fujita, Toshiro
CORPORATE SOURCE: Division of Endocrinology, Department of Internal Medicine, University of Tokyo School of Medicine, Tokyo, 112-8688, Japan
SOURCE: Biochemical and Biophysical Research Communications (2000), 267(2), 632-637
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ***Cancer*** cells metastasized to ***bone*** induce osteoclastogenesis for ***bone*** destruction. Coculture of either mouse melanoma B16 or breast ***cancer*** Balb/c-MC cells with mouse ***bone*** marrow cells (BMCs) induced osteoclast-like cells, which were not obsd. when ***cancer*** cells were segregated from BMCs. Osteoclast differentiation factor (ODF), also known as receptor activator of NF-.kappa.B ligand ( ***RANKL*** ), is a direct mediator of many osteotropic factors. Neither BMCs, B16 nor Balb/c-MC cells alone expressed ODF mRNA. However, coculture of these ***cancer*** cells with BMCs induced ODF expression, which was prevented by indomethacin. Moreover, the coculture with ***cancer*** cells inhibited secretion of osteoprotegerin/osteoclastogenesis inhibitory factor (OPG/OCIF), an inhibitory decoy receptor for ODF, from BMCs. Thus, enhanced osteoclastogenesis in the presence of ***cancer*** cells might be due to an increase in ODF activity. These results suggest that interactions between ***cancer*** cells and BMCs induce ODF expression and suppress OPG/OCIF level in metastatic foci resulting in pathol. osteoclastogenesis

for ***bone*** destruction. (c) 2000 Academic Press.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:311923 BIOSIS
DOCUMENT NUMBER: PREV200100311923
TITLE: Multiple ***myeloma*** disrupts the TRANCE/OPG cytokine axis.
AUTHOR(S): Sordillo, Emilia M. (1); Wong, Brian R.; Liau, Deng F. (1); Colman, Neville (1); Michaeli, Joseph; Choi, Yongwon; Pearse, Roger N.
CORPORATE SOURCE: (1) Department of Pathology, St. Luke's Roosevelt Hospital Center, New York, NY USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 549a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Most patients with multiple ***myeloma*** demonstrate aberrant osteoclast development resulting in severe ***bone*** destruction. We propose that ***myeloma*** triggers ***bone*** ***loss*** both by stimulating stromal expression of TRANCE ( ***RANKL*** /OPGL), a TNF-family cytokine required for osteoclastogenesis, and by decreasing expression of the TRANCE-inhibitor osteoprotegerin (OPG). We used immunohistochemistry and in situ hybridization to evaluate TRANCE and OPG expression in ***bone*** marrow biopsies from 14 ***myeloma*** and 12 nonmyeloma patients (2 MGUS, 2 NHL, 1 CLL, 1 CML, 1 Hodgkin, and 5 normal or reactive). ***Myeloma*** -infiltrated ***bone*** marrow demonstrated increased expression of TRANCE and decreased expression of OPG, a pattern that was not found in ***bone*** marrow infiltrated by non- ***myeloma*** B cell malignancies or MGUS. Differences between the ***myeloma*** and non- ***myeloma*** groups were significant (p = 0.0004 for OPG; p = 0 .0017 for TRANCE). Our in vitro studies also support modulation of TRANCE and OPG by ***myeloma*** . Human ***myeloma*** cell lines induced expression of TRANCE mRNA by stromal cells, and ***myeloma*** -stromal cell cocultures triggered the generation of osteoclasts from murine ***bone*** marrow. Osteoclasts did not develop if a TRANCE antagonist was added to the culture, or if TRANCE-deficient mice were used as the source of stromal cells, confirming the importance of TRANCE to ***myeloma*** -induced osteoclastogenesis. Human ***myeloma*** cell lines also inhibited both constitutive and TGF-beta-induced expression of OPG by human stromal cell lines, indicating suppression of OPG expression by ***myeloma*** . In addition, ***myeloma*** cell lines were found to counteract the ability of exogenous OPG to limit TRANCE-induced osteoclastogenesis. This subversion of OPG function may involve the ability of syndecan-1, expressed at high level on the surface of malignant and non-malignant plasma cells, to bind the heparin-binding domain of OPG. These results indicate that ***myeloma*** disrupts both arms of the TRANCE/OPG cytokine axis, an action which may account for the prevalence and severity of ***bone*** disease in this malignancy.

L7 ANSWER 6 OF 8 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-053099 [04] WPIDS
DOC. NO. CPI: C2000-013803
TITLE: Novel cytokine receptors for regulating osteoclast activity to ameliorate excess ***bone*** ***loss*** effects of osteoporosis, Paget's disease, ***bone*** ***cancers*** etc.
DERWENT CLASS: B04 D16
INVENTOR(S): ANDERSON, D M; GALIBERT, L J
PATENT ASSIGNEE(S): (IMMV) IMMUNEX CORP
COUNTRY COUNT: 87
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9958674 | A2 | 19991118 (200004)* | | EN | 28 |

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB
GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU
LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT UA UG US UZ VN YU ZA ZW
AU 9939888 A 19991129 (200018)
EP 1076699 A2 20010221 (200111) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002514418 W 20020521 (200236) 36

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9958674 | A2 | WO 1999-US10588 | 19990513 |
| AU 9939888 | A | AU 1999-39888 | 19990513 |
| EP 1076699 | A2 | EP 1999-923021 | 19990513 |
| | | WO 1999-US10588 | 19990513 |
| JP 2002514418 W | | WO 1999-US10588 | 19990513 |
| | | JP 2000-548465 | 19990513 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| AU 9939888 | A Based on | WO 9958674 |
| EP 1076699 | A2 Based on | WO 9958674 |
| JP 2002514418 W | Based on | WO 9958674 |

PRIORITY APPLN. INFO: US 1998-110836P 19981203; US 1998-85487P 19980514
AN 2000-053099 [04] WPIDS
AB WO 9958674 A UPAB: 20000124
NOVELTY - Novel soluble ***RANK*** (I) (Receptor activator of NF-KappaB) is made to bind ***RANKL*** (II) ( ***RANK*** -ligand) for regulating osteoclast activity.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the DNA molecule (III) encoding (I) consisting of: (a) a DNA encoding a protein with a fully defined sequence of 616 amino acids (aa) (1) as given in the specification and the protein has a N-terminus consisting of an aa between 1-33 (inclusive) of (1) and a C-terminus consisting of an aa between 196-216 (inclusive); (b) a DNA encoding a protein having an amino acid sequence of
Arg-Met-Lys-Gln-Ile-Glu-Asp-Lys-Ile-Glu-Glu-Ile-

Leu-Ser-Lys-Ile-Tyr-His-Ile-Glu-Asn-Glu-Ile-Ala-Arg-Ile-Lys-Lys-Leu-Ile-

Gly-Glu-Arg (2) and the protein has a N-terminus consisting of an aa between 1-30 (inclusive) of (2) and a C-terminus consisting of an aa between 197-625 (inclusive), of (1); (c) DNA molecules capable of hybridization to the DNA of (a) or (b) under stringent conditins, and which encode (I) that binds to (II); or (d) DNA molecules encoding fragments of proteins encoded by the DNA of (a), (b) or (c), which are fragments of (I) that bind (II).
ACTIVITY - Osteopathic; cytostatic. No supporting data given.
MECHANISM OF ACTION - ***RANKL*** - mediated signal transduction inhibitor.
USE - (I) is used to regulate osteoclast activity (claimed). The therapeutic compositions of (I) or its fragments are useful for regulating an immune or inflammatory response, especially to decrease excess ***bone*** resorption. (I) and its fragments are useful for inhibiting osteoclast activity, regulating osteoclast generation and inhibiting osteoclast generation in individuals inflicted with excess ***bone*** resorption and is used in conjunction with soluble cytokine receptors or cytokines, or other osteoclast/osteoblast regulatory molecules. A composition comprising (I) encoded by (III), when administered into an individual at risk for excess ***bone*** ***loss*** or suffers from a condition of osteoporosis, Paget's disease, ***bone*** ***cancer*** and ***cancers*** associated with hypercalcemia, ameliorates the effects of excess ***bone*** ***loss*** , by binding to (II) and inhibiting binding of other cells expressing ***RANK*** (claimed). It thus decreases osteoclastogeneiss when administered into metastasizing ***cancers*** such as breast ***cancer*** , multiple ***myeloma*** , melanomas, lung ***cancer*** , prostrate, hematologic, head and neck, and renal which metastasize to ***bone*** and induce ***bone*** breakdown by locally disrupting normal ***bone*** remodeling, by distrupting the osteoclast differentiation pathway. This results in the reduction in the number of osteoclasts, lesser ***bone*** resorption and relief from the negative effects of hypercalcemia. (I) ameliorates systemic effects i.e., ***cancers*** associated with hypercalcemia (e.g. squamous cell carcinoma) with excess osteoclast activity, by interfering with I/II signal transduction that leads to the differentiation of osteoclast precursors into osteoclasts.
Dwg.0/0

L7 ANSWER 7 OF 8 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97143233 MEDLINE
DOCUMENT NUMBER: 97143233 PubMed ID: 8989244
TITLE: Serum 1,25-dihydroxyvitamin D may be related inversely to disease activity in breast ***cancer*** patients with ***bone*** metastases.
COMMENT: Comment in: J Clin Endocrinol Metab. 1997 Oct;82(10):3516-7
AUTHOR: Mawer E B; Walls J; Howell A; Davies M; Ratcliffe W A; Bundred N J
CORPORATE SOURCE: University of Manchester Bone Disease Research Centre, Department of Medicine, Manchester Royal Infirmary, United Kingdom.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1997 Jan) 82 (1) 118-22. Journal code: 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219 Last Updated on STN: 19990129 Entered Medline: 19970130
AB 1,25-dihydroxyvitamin D (1,25-(OH)2D) stimulates differentiation and controls proliferation in breast ***cancer*** cells. The role of endogenous 1,25-(OH)2D and its relation to PTH related protein (PTHrP) during the progression of breast ***cancer*** is not known; we therefore investigated these hormones in two studies. In a cross-sectional study of patients with breast ***cancer*** at different stages of disease, serum 1,25-(OH)2D levels (mean +/- SE) were highest in early disease (102 +/- 3.7 pmol/L), fell in normocalemic patients with ***bone*** metastases (52 +/- 5.3 pmol/L; P < 0.01), and were lowest in hypercalcemic patients (33 +/- 5.6 pmol/L; P < 0.001). PTHrP was detectable in the serum of only one normocalcemic patient with progressive metastases but was present in 11 of the 12 hypercalcemic patients, thus PTHrP did not stimulate 1,25-(OH)2D synthesis. In a 6-month longitudinal study of normocalcemic patients with ***bone*** metastases undergoing hormonal therapy, serum 1,25-(OH)2D concentrations fell in patients whose disease progressed (P = 0.0056), but remained constant in those who were stable or responded to treatment. These changes in 1,25-(OH)2D preceded clinical signs of progression and predicted disease response. In the progressive group, five of whom died during the study, 1,25-(OH)2D decreased between the initial and final samples, PTH fell significantly from 24.8 to 13.5 ng/L (P = 0.025), serum calcium rose from 2.27 to 2.39 mmol/L (P = 0.017), and the urinary calcium/creatinine ratio rose from 0.37 to 0.68 (P = 0.046). PTH and 1,25-(OH)2D were significantly correlated in the final samples from this group, Spearman's ***rank*** correlation = 0.80, P = 0.022. The results indicate that normocalcemia in

these patients is maintained, at the expense of suppressing PTH and 1,25-(OH)2D, in the face of increased calcium released from lytic lesions in ***bone*** . ***Loss*** of the antiproliferative effects of 1,25-(OH)2D may then permit more rapid secondary growth of the tumor.

L7 ANSWER 8 OF 8 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 96:753944 SCISEARCH
THE GENUINE ARTICLE: VL701
TITLE: ADVANTAGES OF RALOXIFENE OVER ALENDRONATE OR ESTROGEN ON
NONREPRODUCTIVE AND REPRODUCTIVE TISSUES IN THE LONG-TERM
DOSING OF OVARIECTOMIZED RATS
AUTHOR: SATO M (Reprint); BRYANT H U; IVERSEN P; HELTERBRAND J;
SMIETANA F; BEMIS K; HIGGS R; TURNER C H; OWAN I; TAKANO
Y; BURR D B
CORPORATE SOURCE: ELI LILLY & CO, LILLY RES LABS, LILLY CORP CTR, DEPT
ENDOCRINE RES, MC 797, INDIANAPOLIS, IN, 46285 (Reprint);
ELI LILLY & CO, LILLY RES LABS, LILLY CORP CTR, DEPT STAT,
INDIANAPOLIS, IN, 46285; INDIANA UNIV, SCH MED, DEPT ANAT,
INDIANAPOLIS, IN, 46204; INDIANA UNIV, SCH MED, DEPT
ORTHOPAED SURG, INDIANAPOLIS, IN, 46204
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,
(OCT 1996) Vol. 279, No. 1, pp. 298-305.
ISSN: 0022-3565.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 34
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB For the first time, raloxifene or alendronate was administered to rats immediately after ovariectomy for 10 months and compared with estrogen to elucidate mechanisms behind the raloxifene effects observed in nonreproductive and reproductive tissues. Specifically, 75-day-old rats were randomly selected as sham controls (Sham), ovariectomized controls (Ovx) or ovariectomized rats treated with fully efficacious doses of raloxifene (RA), 17 alpha-ethynyl estradiol (EE2) or alendronate (ABP).
Lumbar vertebrae and proximal tibiae were examined by computed tomography (QCT) and by histomorphometry. Histomorphometry showed differences in ***bone*** architecture between groups when QCT densities were similar, but tibial trabecular ***bone*** analysis by QCT correlated with histomorphometry with r = .86 to .93, depending on the parameter. Both techniques confirmed that Ovx had substantially less ***bone*** than Sham, with greater loss of trabecular ***bone*** in the proximal tibia than vertebrae. Both techniques showed that RA had effects similar to but not identical with EE2 in preventing ***bone*** ***loss*** in vertebrae and tibiae. ABP partially prevented loss of ***bone*** in L-5, but was not significantly different from Ovx in the proximal tibia. This may be caused by ABP suppression of ***bone*** apposition, beyond effects observed for EE2 or RA. RA appeared to be more similar to EE2 because ABP significantly depressed ***bone*** formation ( ***bone*** formation rate, mineral apposition rate) to below RA or EE2 levels, especially in L-5. Mechanical loading to failure of L-6 vertebrae showed a ***rank*** order of vertebral strength of Sham > RA > EE2 > Ovx > ABP, although significant differences were not observed between treatment groups. These data show that ABP suppression of ***bone*** formation can affect ***bone*** quality with long-term treatment. In other tissues, RA had minimal uterine effects, while significantly lowering serum cholesterol to below EE2-treated levels. Both EE2 and RA rats had significantly lower body weights than the other groups. ABP had no effect on serum lipids, uterine weight or body weight. Therefore, RA appears to have a broader range of desirable effects on ***bone*** , body weight, uteri and cholesterol than ABP or EE2 in ovariectomized rats.

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